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CLINICAL STUDIES

CORONARY ARTERY DISEASE

Angioscopic Evaluation of Atherosclerotic Plaques: Validation by Histomorphologic Analysis and Association With Stable and Unstable Coronary Syndromes

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Objectives. **We validated coronary angioscopic observations with histologic assessment of material removed by atherectomy.**

Background. **Up to now, angioscopic findings have been primarily descriptive, and the clinical significance still needs to be substantiated. The proposed Ermenonville classification is relevant but has not yet been validated by histomorphologic analysis.**

Methods. **We compared angioscopic findings in patients with different coronary syndromes and used atherosclerotic material retrieved by directional coronary atherectomy to validate the angioscopic observations. Coronary angioscopy was performed in 63 patients (56 men, 7 women) with stable (26 patients) and unstable angina (37 patients) before and after directional coronary atherectomy. The identity of atherectomized material was confirmed by ex vivo visualization with the angioscope and by postatherectomy angioscopy. Angioscopic and histologic findings could be compared in 44 of 63 patients.**

Results. **Angioscopic findings were grouped into gray-white and yellow lesions (gray-yellow, deep yellow, yellow-red or yellow-pink). We found that patients with unstable angina had predominantly yellow lesions (89%). In patients with stable angina, gray-white (43%) or yellow (57%) lesions were similarly distributed. Ruptured yellow plaques and red or pink thrombi were identified in 11% of patients with stable angina and 39% of patients with unstable or early postmyocardial infarction angina. Histologically, gray-white lesions represented fibrous plaque without degeneration in 64% and with degeneration in 36% of patients. Gray-yellow lesions were associated predominantly with degenerated plaque (64%) and, to a lesser extent, with fibrous plaque (14%) or atheroma (14%). Deep yellow and yellow-red lesions represented either atheroma (53%) or degenerated plaque (42%).**

Conclusions. **Our study establishes a histomorphologic basis for classification and interpretation of angioscopic findings. Yellow plaque color is closely related to degenerated plaque or atheroma and is associated with unstable coronary syndromes.**

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Angiography, the reference standard for evaluating coronary artery disease, and percutaneous transluminal coronary angioplasty have several limitations because of the complex nature of atherosclerosis (1,2). The shadow images obtained by angiography do not fully explain the whole spectrum of morphologic and histopathologic changes, such as fibrous plaque with and without degeneration, atheroma, plaque rupture, thrombus and dissection (3). These different morphologic entities might represent different stages or forms of coronary artery disease with different natural courses. The sensitivity of coronary angioscopy for some of the aforementioned entities has been found to be superior to that of angiography (4–6). Despite its 10-year history (7,8), a thorough histologic analysis has not been performed, and thus the clinical importance of angioscopic findings has not been established. The aims of this study were to investigate different subsets of patients with stable and unstable angina by angioscopy and to validate angioscopic findings by histologic methods using Simpson atherectomy specimens.

Methods

Patients. We performed coronary angioscopy in 63 patients with symptomatic coronary artery disease. The clinical data are summarized in Table 1. All patients underwent coronary angioplasty on the study day by Simpson atherectomy or directional coronary atherectomy. Directional coronary atherectomy was performed immediately after diagnostic coronary angioscopy. Twenty-six patients had stable angina; 24 had postmyocardial infarction angina (myocardial infarction within 3 months); and 13 had rest, crescendo or primary angina. After successful atherectomy, postprocedural angioscopy was performed in the majority of patients (n = 51). Histomorphologic workup was performed in 49 of the 63

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Table 1. Clinical Baseline Characteristics of 63 Patients

Gender	
Male	56 (88.9)
Female	7 (11.1)
Mean age (yr)	58
Range	37 to 81
Symptoms	
Stable angina	26 (41.3)
Unstable angina	37 (58.7)
Crescendo angina	6 (9.5)
Pain at rest	5 (7.9)
Post-MI angina	24 (38.1)
Primary angina	2 (3.2)
Risk factors	
Hypertension	30 (47.6)
Hypercholesterolemia	32 (50.8)
Smoking	34 (54.0)
Diabetes	9 (14.3)

Unless otherwise indicated, data presented are number (%) of patients. MI = myocardial infarction.

patients. The study was approved by the institutional Ethics Committee, and written informed consent was obtained from all patients.

Coronary angiography and atherectomy. Patients were selected for coronary atherectomy according to generally accepted criteria (9,10). Of the 63 atherectomies, 57 were elective, and the remaining 6 were rescue procedures (acute myocardial infarction with failed thrombolysis or failed balloon angioplasty). Target vessels for atherectomy and angioscopy were the proximal and medial left anterior descending coronary arteries (n = 36), the right coronary artery (n = 19), the left circumflex artery (n = 6) and the first diagonal and first marginal branches (n = 2). Most lesions were type B1 or B2, according to the American Heart Association. Mean lesion diameter, as determined by quantitative angiography, was 71% (range 49% to 89%). Fifty-seven patients had Thrombolysis in Myocardial Infarction trial (TIMI) flow grade 2 or 3, and 6 patients had TIMI flow grade 0 or 1.

Coronary angioplasty after diagnostic angioscopy was performed with an atherectomy catheter (Simpson AtheroCath, Devices for Vascular Interventions), mainly using 7F cutters. Eight to 12 cuts were performed in each pass and repeated as necessary. After atherectomy, an adjunctive balloon angioplasty using low pressure (2 to 4 atm) was performed in all patients, irrespective of the angiographic result. Preatherectomy and postatherectomy quantitative coronary angiography was performed in the single most stenotic view with a Philips automatic contour detection system after intracoronary injection of 150 to 250 μg of nitroglycerin.

Coronary angioscopy. In all patients Baxter 4.5F coronary angioscopes (Baxter Healthcare Corporation) were used. After passing the stenosis with a 0.014-in. (0.035-cm) guide wire, the coronary angioscope was introduced into the target coronary vessel. Under fluoroscopic guidance the angioscope was advanced proximal to the stenosis. The lesion was crossed in 37 (59%) of the 63 patients. After blockage of the blood flow with the integrated balloon, the vessel was flushed with 0.5 to 1.0 ml/s of 0.9% saline solution at body temperature until undisturbed vision was obtained. The best images were obtained as the angioscope was slowly withdrawn from the lesion. The duration of angioscopy was limited by the onset of ischemic signs or symptoms (chest pain, electrocardiographic changes). Images were recorded on an S-VHS videotape and reviewed by two experienced operators. Disagreements were solved by discussion. The modified Ermenonville classification was applied to describe the results (11). Angioscopic evaluation focused on lesion surface (smooth or rough), lesion color (gray-white, yellow, yellow-red or yellow-pink) and thrombus (red or pink). In addition to the Ermenonville classification, we differentiated between gray-yellow and deep yellow plaque color.

Histomorphologic analysis. The identity of angioscopically viewed structures and removed specimens for histologic study was confirmed in two ways: 1) by ex vivo angioscopy of the removed material, and 2) by postatherectomy angioscopy, providing evidence of removal of the formerly seen atherosclerotic material.

The tissue samples were fixed in 5% buffered formalin, stained by hematoxylin-eosin, elastin van Giemsa, fibrin and van Kossa. The structure of the vessel wall (intima, media and adventitia), atherosclerotic changes (fibrous plaque, degenerated fibrous plaque and atheroma with or without surface defects) and thrombi were detected by light microscopy. Fibrous plaque was defined as local proliferation of intimal tissue primarily containing connective tissue, irrespective of cell content but without evidence of necrosis. In contrast, degenerated fibrous plaque showed patchy necrosis. Atheroma was characterized by a large, unstructured lipid pool containing cholesterol in the core with a thin or absent fibrous cap (12–14). Samples with mixed histologic findings including atheroma (n = 6), were classified as atheroma. The investigator responsible for histologic analysis was blinded to the angioscopic result and the clinical syndrome.

Statistical analysis. We compared the presenting clinical syndrome with plaque color using the chi-square test. The association between histomorphologic appearance of plaque specimens and angioscopic plaque color was tested by the phi coefficient and Cramers V on the base of a nominal scale using chi-square statistics. A p value <0.05 was considered significant.

Results

Angioscopy. In 59 (94%) of the 63 angioscopic procedures, the quality of the images was acceptable. In four patients the lesion was either not reached (n = 1) or changed by predilation (n = 2), or the image was of poor quality (n = 1).

Colors and surfaces. A smooth gray-white lesion was seen in 24% (14 of 59), a smooth gray-yellow lesion in 25% (15 of 59) and a smooth yellow plaque in 17% (10 of 59) of patients. A rough, ruptured yellow plaque with red lining or protruding thrombus was found in 31% (18 of 59) and a mixed (pink) protruding or occluding thrombus as the predominant finding was obtained in 3% (2 of 59). Typical angioscopic findings are shown in Figure 1.

Figure 1. Typical angioscopic findings. **A,** Smooth, slitlike, gray-white lesion. **B,** Smooth, deep yellow plaque. **C,** Complex, ruptured yellow lesion with red thrombus. **D,** Protruding pink (mixed) thrombus.

Findings in different coronary syndromes. Lesion color was similarly distributed among patients with stable angina (57% yellow and 44% gray-white), whereas in patients with unstable angina and postmyocardial infarction angina, the predominant color was yellow (89% unstable angina and 91% postmyocardial infarction). The color difference in stable versus unstable angina pectoris was highly significant (chi-square test, $p \leq 0.004$; likelihood ratio, $p \leq 0.005$). Lesion surface was also different in patients with stable versus unstable angina. Ruptured surfaces were found in 26% of stable angina, 39% of unstable angina and 44% of postmyocardial infarction patients. For detailed results see Table 2 and Figure 2.

Histomorphologic analysis. In 49 of the 63 patients who underwent diagnostic angioscopy followed by atherectomy, the removed material was analyzed by histomorphologic methods. In this group 20 patients had stable angina and the other 29 had unstable angina (18 of them with postmyocardial infarction angina).

On histologic study three different plaque entities were found (Fig. 3): 16 fibrous plaques, 21 degenerated fibrous plaques and 12 atheroma. Partially organized thrombi accompanied the lesions in 12 (25%) of 49 patients.

Comparison of histomorphologic and angioscopic findings. *Validation results.* Of the 49 histopathologic samples, 44 could be compared with angioscopic findings. Five discrepant cases were excluded after performing ex vivo angioscopy of the removed material or postatherectomy angioscopy. Ex vivo examination of the material, which was performed in all patients, revealed conflicting colors and surface structure in three patients. In two patients, red or pink thrombi on the surface prevented angioscopic assessment of the underlying plaque.

In addition, in two patients the plaque material was sparse, and thus plaque color could not be clearly determined ex vivo. In one patient suboptimal image quality during the ex vivo evaluation prevented unequivocal assignment. These three patients were also evaluated by post-directional coronary atherectomy in vivo angioscopy (as discussed subsequently), which revealed cuts or grooves within the plaques visualized previously.

Of the 44 patients who passed the ex vivo validation procedure, 36 were further evaluated by post-directional coronary atherectomy angioscopy within the target vessel segment. Three patients, in whom ex vivo angioscopy revealed concordant findings, did not have acceptable image quality. Thirty-three patients presented with either extraction of the plaques visualized previously or cuts or grooves within these plaques.

Thus, in each patient at least one validation procedure confirmed identity of the visualized and histologically investigated material, and in 33 of 44 patients both validation methods were successful.

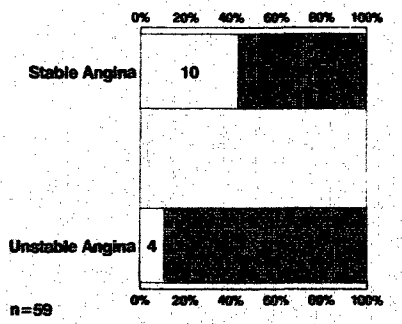
Results of the comparison. The main plaque colors (gray-white, gray-yellow and deep yellow or yellow-red) were compared with the three main histological subgroups (fibrous plaque, degenerated fibrous plaque and atheroma with or without surface defects). Gray-white lesions (n = 11) represented fibrous plaque without degeneration in 64% and with degeneration in 36% of patients. Gray-yellow lesions (n = 14) were associated predominantly with degenerated plaque (64%) and in a minority of patients with fibrous plaque (n = 3) or atheroma (n = 2). Deep yellow or yellow-red lesions (n = 19) represented either atheroma (53%) or degenerated plaque (42%). The associations between angioscopic color and the

Table 2. Clinical and Angioscopic Findings in 63 Patients Before Coronary Atherectomy

Angioscopic Lesion	Stable Angina	Unstable Angina		
		Total	Post MI	Rest, Crescendo and Primary Angina
Smooth, gray-white	10	4	2	2
Smooth, gray-yellow	4	11	6	5
Smooth, deep yellow	3	7	5	2
Ruptured, yellow-red	6	12	8	4
Ruptured, yellow-pink	—	2	2	—
Not assessable	3	1	1	—
Total	26	37	24	13

Data presented are number of patients. MI = myocardial infarction; — = none found.

Figure 2. Distribution of gray-white (**open boxes**) and yellow (**cross-hatched boxes**) color in plaques of patients with stable and unstable angina (chi-square test, $p \leq 0.004$; likelihood ratio, $p \leq 0.005$).



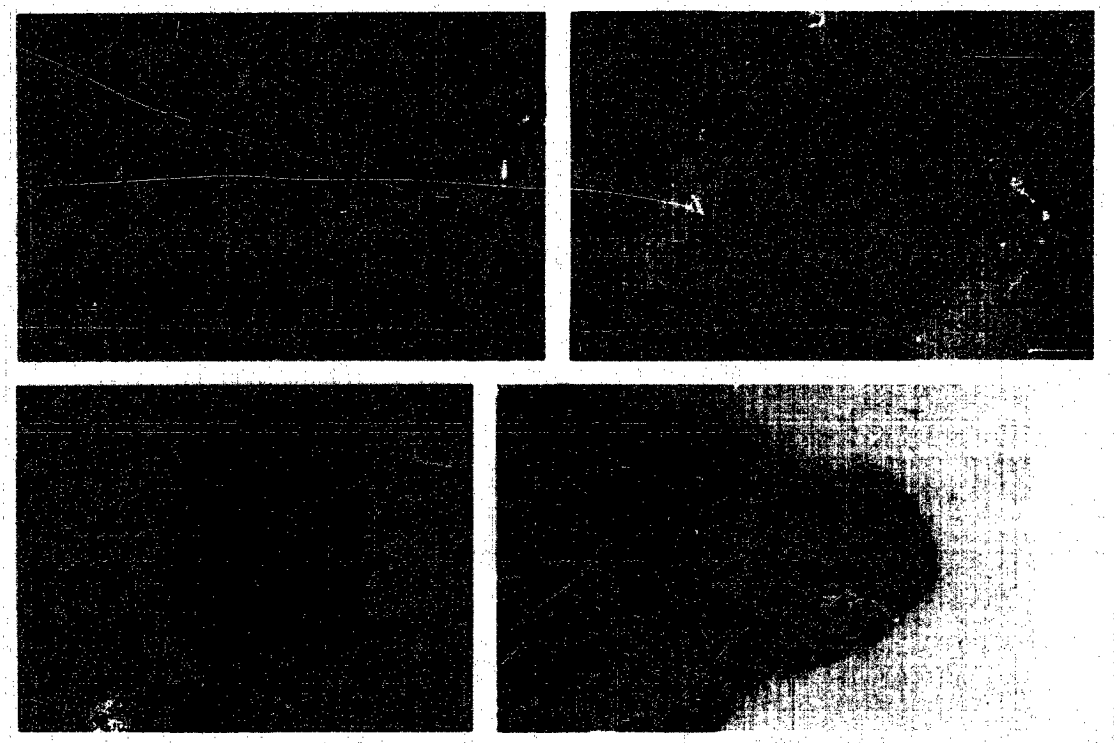


Figure 3. Histomorphologic entities of analyzed atherectomy specimens. **A,** Fibrous plaque. **B,** Degenerated fibrous plaque. **C,** Atheroma. **D,** Mixed thrombus.

absence or presence of atheroma (phi coefficient 0.51, Cramer's V 0.51), as well as the absence or presence of fibrous plaque (phi coefficient 0.54, Cramer's V 0.54, were both significant (both $p < 0.003$) (Fig. 4).

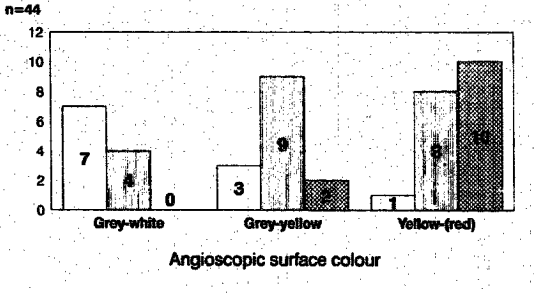
In 16 of 44 angioscopic findings, red or pink color was present. In 50% of these patients (8 of 16) a red or pink thrombus incorporated into the plaque was found by histomorphologic study. In 24 (86%) of 28 patients with smooth plaque and absence of red or pink color, no thrombus was found by histologic analysis, whereas in 4 (14%) of 28 patients, thrombus was detected only by histomorphologic analysis. Superficial thrombi were not evaluated because a periprocedural or postprocedural development could not be excluded.

Complication rate of diagnostic angioscopy. No major complication (myocardial infarction, need for rescue angioplasty or coronary artery bypass grafting, death) occurred as a result of angioscopy. Three of the 63 patients (5%) had minor complications—one patient developed bradycardia requiring temporary pacing, and the other two patients revealed small intimal lesions (type A dissection) at the site of the inflation cuff. They remained free of clinical or angiographic sequelae at 6-month follow-up.

Discussion

A major discrepancy between the lesion severity found on angiography and postmortem findings has been published (1,2), and atherosclerotic processes are more complex than revealed by the shadow images of angiography. A wide variety of histologic changes are found in human atherosclerosis—fibrous plaques, degeneration within fibrous plaques, atheroma, plaque rupture, white and red thrombus, dissections and others (3). These are of the utmost importance for clinical symptomatology and disease progression (15).

Figure 4. Validation of coronary angioscopic findings. Comparison with histomorphologic entities of 44 atherectomy specimens. **Open bars** = fibrous plaque; **striped bars** = degenerated fibrous plaque; **crosshatched bars** = atheroma.



Percutaneous coronary angioscopy offers the unique ability to view the endoluminal surfaces of coronary arteries and to identify these different entities; plaque surface and color (16), fissuring of plaque, plaque ulcera and dissections (4,17) as well as white, red and mixed thrombi (18,19) can be identified. Since its introduction 10 years ago, coronary angioscopy has been used as a diagnostic tool (16) and to guide coronary angioplasty (20–22). A first standardization of angioscopic findings was proposed in the Ermenonville classification (11). This classification represents a descriptive analysis of findings regarding color and surface of the endoluminal vascular wall. It does not include validated histologic entities. So far, comparisons of angioscopy and histology have been sparse (23) and largely performed on postmortem arterial segments (24). Our investigation was performed to validate coronary angioscopic findings by histologic analysis, which was possible by combining Simpson atherectomy with coronary angioscopy. In addition, we present angioscopic findings in different clinical syndromes of coronary artery disease and angina pectoris.

Importance of plaque color and surface. Gray-white lesions were predominantly correlated with fibrous plaque, mostly without degenerations. Lesions of yellow color represented either degenerated fibrous plaque or atheroma. Furthermore, pale yellow or gray-yellow lesions were mostly found in degenerated plaque, whereas deep yellow and yellow-red lesions were correlated with atheroma. Gray-yellow and deep yellow lesions were often found to have irregular or ruptured surfaces and contained red or pink areas. Gray-white lesions were usually smooth and never contained red or pink areas.

Plaque color and morphology were different in patients with stable and unstable angina. In stable angina both types of lesions—smooth gray-white and yellow lesions—were found to be equally distributed. In the patients with unstable angina and postmyocardial infarction the yellow color was found to be highly predominant (9:1).

There are only a few reports on the importance of yellow vessel wall color. Hosokawa and Suzuki (25) performed angioscopy in 20 patients with acute myocardial infarction and detected yellow plaques in 59% of the patients, all of whom presented with evidence of red thrombus. Waxman et al. (26) found a yellow plaque underlying an angioscopically detectable thrombus in 68% of patients and associated the yellow color with the risk of plaque rupture. A predominance of smooth gray-white lesions in patients with stable angina pectoris was also reported by Mizuno et al. (16). Ruptured complex plaques with ulceration, fissures and appositional thrombus were also found in unstable angina pectoris by several investigators (26,27). In contrast to these investigations, we found a high proportion of yellow lesions in patients with stable angina (56%). In part, this may result from a relatively high percentage of patients in whom angioscopy of a postinfarction coronary vessel was performed. By definition, infarct-related arteries in patients with stable angina were determined as stable 3 months after myocardial infarction.

Patients with stable angina without a prior myocardial infarction, with stable angina with a myocardial infarction >3 months previously and with a myocardial infarction ≤3 months had yellow plaques in 40%, 69% and 91%, respectively, and ruptured surfaces in 20%, 31% and 43%, respectively. Thus, plaque color seems to be a major indicator of instability and acute complications of coronary artery disease. This finding correlates well with histopathologic evaluations of postmortem vessels. A large lipid pool in the plaque center is associated with plaque rupture (14), and a wide majority of lesions from patients with recent thrombotic occlusions of the coronary arteries show hemorrhage into the plaque, in contrast to patients with innocuous plaque (12).

Histomorphologic validation of thrombi. Thrombi have been found by angioscopic investigations in only a small proportion of patients with stable angina, although in patients with acute coronary syndromes (16) different colors (white, pink and red) and different sizes of thrombi (just covering the vessel surface, protruding or even occluding) have been described (6,19). A high percentage of thrombi has been found by several investigators, especially in patients in unstable angina (18,19,28). The crescendo type of unstable angina has been associated with white thrombi (19,29), whereas rest and postmyocardial infarction angina has been linked to red and pink thrombi (18). In support of this, we found an increased frequency of yellow-red and yellow-pink lesions in unstable as compared with stable angina. However, histologically, validation of thrombus is much more difficult than of the underlying atherosclerotic material, because thrombi are highly sensitive to the extraction procedure during atherectomy (especially white thrombi). As long as they are solely located on the surface of the plaque, they are difficult to distinguish from thrombi developing during the extraction or even the angioscopy procedure. Therefore, this first investigation of the histology of angioscopic findings was mainly aimed at differentiating the underlying plaques.

Study limitations. One general limitation of this study is the incomplete vessel wall visualization. In addition, not all stenoses could be crossed with the angioscope. Thus, images of the atherosclerotic lesions were incomplete. We tried to minimize this problem by evaluating the extracted material ex vivo and by reevaluating the coronary vessel angioscopically after atherectomy to assure that the target material had in fact been successfully extracted. Only investigations in which at least one of these validation procedures had been successfully performed and undoubtedly showed identity of the extracted material with visualized plaque were subjected to histopathologic comparison.

A second limitation is that the atherectomy itself, with cutting and storing of the material in a small catheter chamber, may traumatize the material and alter the integrity of the plaque. Therefore, a systematic histopathologic comparison of thrombi found on angioscopy has not been attempted in this investigation. Furthermore, the differentiation of white, very mobile material is difficult. Often the material is very small and constitutes only a minor part of the total material removed. The differentiation between white thrombi and white plaque material is not possible in all cases. We identified white thrombi as similar

to milk glass—that is, light white, very mobile structures within the lumen, on top of plaques or even on the guide wire.

Clinical implications. Despite these limitations, a very clear association could be found between gray-white lesions and fibrous plaque, and between yellow lesions and plaque degeneration or atheroma. In addition, plaque rupture and superimposition of thrombus were correlated with yellow lesions. Yellow lesions and plaque rupture were predominantly found in unstable angina. This association, which cannot be appreciated by either angiography or intravascular ultrasound, might, especially in low grade lesions, have considerable impact on therapy. The yellow color probably indicates the presence of a thin fibrous or merely endothelial layer covering free lipids. In contrast, thrombi that have been identified on the surface of plaque in earlier angioscopic studies probably represent the product of yellow lesion rupture. These thrombi are highly variable during the time when the ruptured plaque is subjected to healing and endothelial coverage. Spontaneous or therapeutically induced changes in coagulation and thrombolysis might also influence the appearance of thrombi.

The similar distribution of gray-white and yellow lesions in patients with stable angina could be an indication of dissimilar progression rates of coronary artery disease. Yellow lesions may represent a more progressive form of the disease with a higher risk of plaque fracture. Therefore, implications on prognosis will be investigated in further studies. Another interpretation could be that the color might represent different time windows during the development of atherosclerosis or during the healing processes of plaques. In any case, the potential to differentiate similar lesions on angiography and intravascular ultrasound by means of angioscopy opens an interesting arena for further investigations.

Conclusions. Coronary angioscopy allows further differentiation of coronary atherosclerotic lesions found on angiography. Angioscopic results are highly predictive of different types of histomorphologic lesions. The lesion types identified during angioscopy correlate with either unstable angina or postmyocardial infarction angina (yellow and yellow-red lesions) or with stable angina (gray-white lesions). Angioscopy is a useful tool in determining coronary pathology. Our findings justify a prospective effort to investigate the impact of angioscopic findings on the course and complications of coronary artery disease.

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